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An Improved Preparation of Tris(ethylenedioxyboryl)methane, a Reagent for the Homologation of Aldehydes and Ketones

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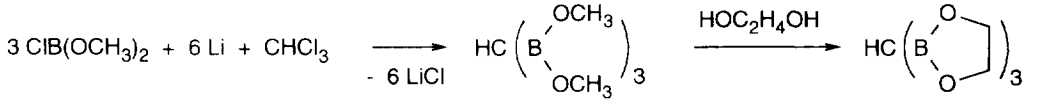
Abstract: The preparation of tris(ethylenedioxyboryl)methane (**2**), the reagent for the only known homologation of aldehydes and ketones under non-acidic conditions, was improved by avoiding the difficult isolation of the intermediate tris(dimethoxyboryl)methane (**1**) and by direct crystallization of **2**.

During our attempts to homologate an aldehyde group in an acid-sensitive macrolide derivative[1], we learned that most of the commonly used homologating agents such as the Wittig- or Wittig-Horner reagents phosphines[2], phosphonates[3], and phosphine oxides[4] as well as chloromethyltrimethylsilane[5] require acidic hydrolysis in the second step to liberate the aldehyde. Only one method has been described for homologation of aldehydes under non-acidic conditions which applies lithium bis(ethylenedioxyboryl)methide (**3**) in a boron-analogous Wittig reaction[6-8]. Though this seems to be an important alternative, especially for the synthesis of natural products with sensitive functionality, to our knowledge only the authors themselves have used it to date. The authors also concede[8]: "The major disadvantage of this new method is the inconvenience of preparing tris(ethylenedioxyboryl)methane (**2**)."



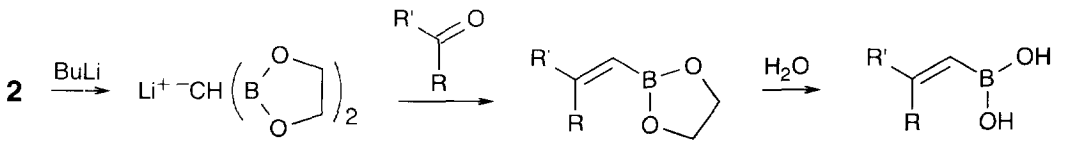
1 **2**

According to the procedures described[6,7], tris(ethylenedioxyboryl)methane (**2**) is synthesized in two steps from dimethoxyboron chloride, chloroform, and lithium. The major difficulty is the isolation of the

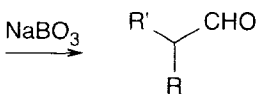
intermediate tris(dimethoxyboryl)methane (**1**) from the crude product. Careful work up and rapid distillation is required to avoid total decomposition of **1** caused by some by-products[7] followed by a second distillation step. In addition, **2** has to be purified by vacuum sublimation at 0.02 mbar.

Our attempts to reproduce the synthesis of **1** resulted, in the best case, in a yield of 5 % of impure **1**. Transesterfication and sublimation yielded a small amount of **2** which inevitably was contaminated with ethylene glycol, as well as other volatile by-products, and was not useful for the desired purpose.

During these experiments three critical points were identified: the elimination of large amounts of lithium chloride and other insoluble by-products in the first step, thermal stress during distillation of **1** and the separation of **2** from excess ethylene glycol. After some experimentation we found, that starting with hexane prewashed dispersed lithium, the lithium chloride and polar by-products can be precipitated from the filtrate of the reaction mixture by addition of hexane while **1** remains in solution. After transesterification of crude **1** with ethylene glycol, **2** is pure enough to be crystallised from hot THF. **2** forms colourless crystals with m.p. 179-181 °C (lit.[7]: 170-172 °C).



3 **4** **5**



6a R = $Ph(CH_2)_3-$, R' = H

6b R,R' = $-(CH_2)_5-$

To test the performance of this material, 3-phenylpropionic aldehyde and cyclohexanone were homologated according to the general procedure described[8]. The formation of the intermediate **4** was monitored by ^1H NMR and found to be incomplete after 3 hours. After 18 hours, aqueous work up, oxidation with aqueous sodium perborate solution, and purification by column chromatography yielded 85 % of 4-phenylbutyric aldehyde (**6a**) and 65 % cyclohexane aldehyde (**6b**).

Similarly keto and aldehyde groups in acid sensitive soraphen derivatives were homologated in good yields[1,9]. In this case the oxidative liberation of the aldehydes was achieved under very mild conditions with an excess of sodium perborate in THF/MeOH/H_2O at pH 9.

Alternatively the intermediate alkenylboronic ester **4** or acid **5** may be used for a *Suzuki* vinyl coupling without purification in a one-pot reaction. The utility of this reaction is under investigation.

We hope that the reliable and simple preparation of pure tris(ethylenedioxyboryl)methane (**2**) described here may eventually lead to a broader application in organic synthesis.

Experimental

NMR: WM 400 and AM-300 spectrometers (Bruker), ^{1}H: 400 and 300 MHz, ^{13}C: 75.5 MHz, internal standard TMS. - Mass spectroscopy: EI/FAB: spectrometer MAT 95 (Finnigan). - GC: GC-6000 (Carlo Erba); DB 5 column, 30 m, 0.25 mm (J&W Scientific). - Melting points: Büchi 510 melting point apparatus, uncorrected.

Tris(ethylenedioxyboryl)methane (**2**): 37.6 g (0.32 mol) of boron trichloride was condensed into a 250 ml flask under nitrogen at -50 °C. 66.7 g (0.64 mol) of trimethyl borate was added with stirring at this temperature over a period of 5 min to form the dimethoxyboron chloride. After warming up to room temperature, 38.2 g (0.32 mol) chloroform was added and the mixture transferred to a 250 ml dropping funnel. In a 1-liter three-necked flask, 40 g lithium dispersion (30 % in mineral oil) was washed twice with each 100 ml dry hexane under nitrogen to give 12.0 g (1.73 g-atoms) of lithium powder after drying at 12 mbar vacuum. The flask was fitted with a Teflon-paddle stirrer, an internal thermometer, and the dropping funnel. 500 ml of dry THF was added to the lithium, the slurry was cooled to -40 °C and the mixture of dimethoxyboron chloride and chloroform was added over a period of one to two hours. The temperature was kept at -40 to -30 °C and vigorous stirring was maintained during the addition. The mixture was allowed to warm up over two hours to room temperature, filtered under a stream of nitrogen through a Büchner funnel with a D2 sinter plate (7 cm), and the residue was washed with 50 ml of dry THF (CAUTION: The residue may be pyrophoric and is best disposed of in a large volume of water before all the solvent evaporates). The filtrate was concentrated in vacuo to ~200 ml and mixed with 100 ml of dry hexane. The precipitate formed was removed by filtration. The filtrate was evaporated and the residue was shaken vigorously with 60 ml of diethyl ether. The slurry was filtered and the filtrate was concentrated to dryness in vacuo to yield 42.8 g of crude tris(dimethoxyboryl)methane (**1**). The latter was dissolved in 100 ml THF, cooled to 0 °C and 28 g (0.45 mol) ethylene glycol was added. After stirring for 30 min at this temperature, the solvent was evaporated. The residue was heated at 2 mbar to 70 °C to remove most of the excess of ethylene glycol and volatile by-products to yield 43.0 g of crude product. This was dissolved in 100 ml of boiling THF, filtered, and cooled down to 5 °C. After one to three days at 5 °C, 6.5 g of colorless crystals of **2** (m.p. 179-181 °C) were collected. The mother liquor was concentrated to about half of the volume and kept again at 5 °C for several days to yield a second batch of 3.7 g of **2** (m.p. 170-175 °C). The total yield was 10.2 g (16 %). The spectroscopic data agree with those of ref.[7]. The product is stable at room temperature, although hygroscopic.

4-Phenylbutyric aldehyde (**6a**): 316 mg of **2** (1.4 mmol) was dissolved in 3 ml dichloromethane and 3

ml THF. The solution was cooled to -70 °C, 0.72 ml of a 1.6 M solution of butyl lithium (1.2 mmol) in hexane was added and the mixture was stirred for 2.5 h. 94 mg of 3-phenylpropionic aldehyde (0.7 mmol) was added at this temperature. After warming up, the solution was stirred for 18 h at room temperature. The solvents were evaporated and the residue was dissolved in a mixture of 3 ml dichloromethane and 3 ml aqueous pH 10 buffer. The mixture was stirred vigorously and 462 mg of sodium perborate tetrahydrate (3 mmol) was added in several portions over a period of one hour. The solution was diluted with brine and extracted three times with dichloromethane. The combined organic layers were dried with sodium sulfate and the solvent was evaporated. 1 % of reactant was estimated by GC analysis of the crude product. Further purification by column chromatography (Si 60, eluent dichloromethane) yielded 88 mg (85 %) of **6a**.

Cyclohexanecarboxaldehyde (**6b**): 69 mg of cyclohexanone (0.7 mmol) was homologated as described above to yield after purification 51 mg (65 %) of **6b**.

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References and Notes

1. Schummer, D; Jahn, T.; Höfle, G. *Liebigs Ann. Chem.* **1995**, 803-816.
2. Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150-6151; Wittig, G.; Knaus, E. *Angew. Chem.* **1959**, *71*, 127.
3. Kluge, A. F. *Tetrahedron Lett.* **1978**, *39*, 3629-3632.
4. Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, *99*, 314-315.
5. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 4536-4537.
6. Matteson, D. S.; Moody, R. J.; Jesthi, P. K. *J. Am. Chem. Soc.* **1975**, *97*, 5608-5609.
7. Matteson, D. S. *Synthesis* **1975**, 147-158; Matteson, D. S.; Jesthi. P. K. *J. Organomet. Chem.* **1976**, *110*, 25-37.
8. Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091-1095.
9. Jahn, T. Doctoral Thesis, Technical University of Braunschweig, **1995**.

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